IN THE DRAWINGS:

Please replace original figure 9 (2 pages) with the replacement Figure 9A-B submitted herewith. A version showing the revision to Figure 9 (denoting the first page as "FIGURE 9A" and the second page as "FIGURE 9B") marked in red is also enclosed.

REMARKS

Claims 61- 69 are pending. Claims 74 and 75 are cancelled without prejudice as redundant over the amended claims.. Claims 61, 62, and 64-69 are amended to more particularly state and distinctly claim the subject matter that Applicants regards as their invention. Amendments to the claims do not introduce new matter and are fully supported by the specification as filed. The specification has been amended to address objections raised by the Examiner.

Claims 61-69 and 74-75 are rejected for alleged lack of enablement under 35 U.S.C. § 112, first paragraph. Claims 61, 62, 67-69, 74 and 74 are rejected under 35 U.S.C. § 103(a) for alleged obviousness. For reasons set forth below, it is respectfully requested that the objections to the specification and rejections of the claims be withdrawn.

1. Objections To The Specification And Declaration Should Be Removed

The specification is objected to because, according to the Examiner: (i) the abstract does not describe the elected subject matter; (ii) the title is not descriptive; (iii) Fig. 1 and 9 are not properly labeled; (iv) the Sequence Listing fails to comply with the requirements of 37 C.F.R. §§1.821-1.825; and (v) the specification does not properly indicate the relationship to a parent application. The Declaration is contended to be defective due to an improper claim of priority.

In response Applicants have:

(i) amended the abstract to describe the elected subject matter;

(ii) amended the title to describe the subject matter;

(iii) amended the specification and Figure 9 so that:

(a) the specification at page 5 is amended to correctly list all parts of FIGURE 1 i.e. FIGURE 1A- E;

(b) Figure 9 is revised by providing herewith separately labeled substitute drawing sheets Fig. 9A and 9B, and

(c) the description of Figure 9 in the specification is amended to reflect that Figure 9 has two subparts; and

(iv) amended the description of Fig 1C to specify sequence identifiers for the sequences disclosed therein.

The sequence listing filed with the application contains listings corresponding to SEQ ID NOS: 4 and 5, disclosed in Fig. 1C. Applicants believe that a substitute Sequence Listing is not required since the aforementioned amendment to the specification brings the Application in compliance with 37 C.F.R. §§1.821-1.825.

As regards the priority claim, Applicants assert that it is correct. The instant application is a continuation of its PCT parent, which in turn is a continuation-in-part of grandparent U.S. Application Ser. No. 09/948,227. It is believed that no revision of the specification or supplemental Declaration should be necessary.

2. **The Claims Satisfy The Enablement Requirement**

Claims 61-69 and 74-75 are rejected under 35 U.S.C. § 112, first paragraph under the enablement requirement.

The Examiner lists the following bases for rejection of claims under factors relating to "state of the art/unpredictability" (pages 5-7, Official Action mailed June 8, 2006):

(i) at the time of filing the phenotype of transgenic animals was unpredictable;

(ii) a number of limitations in producing non-mouse transgenic animals existed at the time of filing; and

(iii) the art at the time of filing did not teach the function of PCTA-1 *in vivo* .

In enumerating grounds for rejection based on "teachings in the specification," the Examiner contends that (pages 7-11, Official Action mailed June 8, 2006):

(i) the specification does not teach how to use the claimed animals as models of malignancy, and since the PCTA-1 animals do not have a demonstrable phenotype it would be unduly burdensome to determine a phenotype (page 8, Official Action mailed June 8, 2006);

(ii) No guidance is provided to use singly or double transgenic animals since: (a) PCTA-1 transgenic mice crossed with TRAMP mice fail to produce detectable tumors; (b) no further use for the PCTA-1/TRAMP mice is taught; (c) the use for singly transgenic PCTA-1 mice is not readily apparent; and (d) double transgenic animals are not claimed (pages 8-9, Official Action mailed June 8, 2006);

(iii) the specification does not provide adequate guidance as claimed (claim 61) to produce a transgenic non-human animal whose cells comprise the nucleic acid encoding SEQ ID NO:3 (page 10, Official Action mailed June 8, 2006);

(iv) The specification does not provide support for claim 67 which claims any kind of PCTA-1 (page 10, Official Action mailed June 8, 2006);

(v) The specification does not provide support for claim 68 which claims increased activity of any human PCTA-1 (page 10, Official Action mailed June 8, 2006);

(vi) The specification does not provide support for claim 68 which encompasses increasing levels of PCTA-1 other than by transgenic methods (page 11, Official Action mailed June 8, 2006);

(vii) The specification does not provide support for claim 69 which encompasses administering a compound to a transgenic animal to increase PCTA-1 expression (page 11, Official Action mailed June 8, 2006).

Applicants have cancelled claims 74 and 75 rendering any rejection directed to those claims moot. Claims 61-62 and 64-69 are currently amended to limit the claims to a transgenic mouse, thus obviating the grounds for rejection based on the unpredictability and difficulty to produce non-murine transgenic animals (points (A) (i) and (A) (ii) above).

In response to rejection of claims due to lack of teachings of the function of PCTA-1 *in vivo*, Applicants assert that the present specification provides the necessary guidance to a skilled practitioner so that the rejection should be withdrawn. Based on *in vitro* studies PCTA-1 was shown to possess tumor suppressive activity in transformed cells (Figure 8A-B, specification at page 32, lines 8-28). A person of ordinary skill would know that tumor suppression would be an expected phenotype *in vivo*. Applicants have used *in vivo* PCTA-1 expressing transgenic mice to perform tumorigenesis studies on doubly transgenic PCTA-1/TRAMP mice. Applicants show that expression of PCTA-1 in doubly transgenic mice suppresses tumor formation *in vivo* (page 39, line 31 through page 40, line 4). The TRAMP model is well established as generating tumors at a 100%

frequency in mice carrying the TRAMP transgene (see reference nos. 71 and 87 in the Information Disclosure Statement). A person of ordinary skill would know that exogenous tumor suppressor activity would be required to suppress TRAMP tumorigenesis. This function is clearly provided by PCTA-1 in the double transgenics thereby traversing the Examiner's rejection (point (A) (iii) above) that the *in vivo* activity of PCTA-1 is unknown.

The Examiner states that a lack of phenotype of PCTA-1 transgenic mice places undue burden on a person of ordinary skill to use the animal. Applicants note that the lack of an overt phenotype provides a transgenic animal that closely resembles a non-transgenic normal animal. Such an animal in fact provides a powerful research tool for specific purposes (enumerated below), as opposed to an animal showing deleterious side effects due to expression of a transgene. This utility will be easily appreciated by a skilled practitioner, and is clearly described in the specification (page 23, lines 24-34, page 24, lines 1-2, page 40, lines 1-4). The Examiner alleges further that no guidance is provided to use singly or double transgenic animals. The specification discloses that PCTA-1 transgenic mice crossed with TRAMP mice do not produce detectable tumors in the same timeframe that singly transgenic TRAMP mice have externally palpable tumors (page 40, lines 1-4). It is well known that TRAMP tumorigenesis displays a 100% penetrance in transgene positive male mice (reference nos. 71 and 87 in the Information Disclosure Statement). A skilled artisan will know that doubly transgenic PCTA-1/X mice (where X=any mouse model of generalized or tissue specific tumorigenesis) provides a powerful model to study the mechanisms underlying oncogenesis and tumor spread (specification at page 22, lines 19-31), and to identify agents that enhance tumor

suppressive effects (specification at page 23, lines 30-34, and page 24, lines 1-2). Thus contrary to the Examiner's basis for rejection, utility for the PCTA-1/TRAMP or PCTA-1/X mice is taught, and the use for singly transgenic PCTA-1 mice is clearly evident i.e. for creating doubly transgenic PCTA-1/X animals. Applicants respectfully disagree that doubly transgenic animals are not claimed since the animals of claims 64-65 represent doubly transgenic mice culminating in a mouse equivalent to a PCTA-1/TRAMP double transgenic as specified by the mouse of claim 66. Based on the above arguments Applicant's assert that the claims 61-66 are fully enabled by the specification as filed so that the rejections summarized in points B (i) and B (ii) above should be withdrawn.

The rejection of claims 61, 67-69 are obviated following amendments that more particularly state and distinctly claim the subject matter claimed therein. Thus amendment of claim 61 and its dependent claims to limit the non-human transgenic animal to a transgenic mouse removes the grounds the based on alleged on lack of support of any non-human transgenic animal. Amendment of claim 67 to specify a PCTA-1 species having the sequence of SEQ ID NO:6 obviates the grounds for rejection due to lack of support of any kind of PCTA-1 species or isoform. Limitations have been introduced in to claims 68 and 69, specifying the type of PCTA-1 (SEQ ID NO:6), and correlates increased level or activity of PCTA-1 to transgene expression. These amendments remove grounds for rejection for alleged lack of support for any PCTA-1 species or unsupported method for increasing PCTA-1 levels or activity.

In light of the above statements, Applicants assert that claims 61-69 are fully enabled, and the rejections under 35 U.S.C. § 112, first paragraph should be withdrawn.

3. **The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn**:

Claims 61, 62, 67-69, 74 and 75 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Kasper *et al.* (Laboratory Invest. 78(3):319-333, 1998; henceforth *Kasper*) in view of Su *et al.* (Proc Natl Acad Sci USA 93:7252-7257, 1996; henceforth *Su*).

According to the Examiner *Kasper* teaches a transgenic mouse comprising rat prostate tumor-specific antigen (probasin) operably linked to a promoter, that is to say, a transgenic mouse overexpressing probasin. Su teaches a nucleic acid sequence of SEQ ID NO:3. The combination of both references, according to the Examiner, render the construction of a PCTA-1 transgenic mouse obvious. The Examiner states that:

> "[I]t would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse whose genome comprised a prostate tumor antigen from a non-mouse species as taught by Kasper, wherein the prostate tumor antigen was the human prostate carcinoma antigen encoded by SEQ ID NO: 3 taught by Su. One of ordinary skill in the art at the time of filing would have been motivated to replace the rat prostate tumor antigen used by Kasper with the human prostate tumor antigen taught by Su to determine the function of PCTA-1 in vivo. The specification teaches transgenic mice comprising SEQ ID NO: 3 did not have altered phenotypes (pg 39, lines 6-18). Therefore, the combined teachings of Kasper and Su are no less than the teachings in the specification."

Applicant's assert that there is no prima facie basis for rejection of the claims under 35 U.S.C. § 103(a). Rejection of cancelled claims 74 and 75 is rendered moot. Applicants note that the present claims are directed to a transgenic PCTA-1 expressing mouse which has utility to study tumorigenesis and identify treatment agents.

Applicant's respectfully disagree with the Examiner's conclusion that construction of the PCTA-1 transgenic mouse was merely to determine its function *in vivo*. The phenotypic effect of PCTA-1 expression was already established from earlier studies and construction of the mouse model was rationally based on the utility of a tumor suppressing mouse model. In contrast to the claimed invention, the mouse of *Kasper* displays an overt, self-generating prostate tumor phenotype (see *Kasper*, Figure 1 at page 321. and final paragraph of discussion at page 330). In fact, *Kasper* utilize the rat probasin promoter sequence to drive tissue specific expression of a non-prostate gene (SV-40 large T-antigen) unrelated in any way to the PCTA-1 or other human or mouse prostate specific gene. There would be no rational basis to combine the disclosures of *Kasper* and *Su* due to the fundamentally distinct nature of the combination compared with the presently claimed invention. First, a mouse based on *Kasper* would only have restricted prostate specific expression. An important basis of the present invention is to be able to study several tumor types (specification at page 24, lines 1-2) which preferably requires ubiquitous PCTA-1 transgene expression. Second the overt self-generated (autochthonous) phenotype of the transgenic mouse in *Kasper* is tumorigenic, as opposed to tumor-suppressive. The tumorigenic phenotype would preclude the type of studies made possible by crossing specific tumor mouse models with PCTA-1 transgenic mice claimed herein.

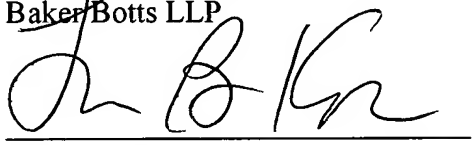
Therefore contrary to the Examiner's assertion the Applicant's claimed invention is not *prima facie* obvious over the combination of cited references, and differs so fundamentally as to not satisfy any obviousness determining criteria. The rejection under 35 U.S.C. § 103(a) should therefore be withdrawn.

Conclusion

Applicants respectfully request entry of the foregoing remarks in the file history of this application. It is respectfully requested that the rejections of the claims be withdrawn. An early allowance is earnestly solicited.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication or refund any overpayments to Deposit Account No. 02-4377. A duplicate of this sheet is enclosed.

Respectfully submitted,
Baker Botts LLP



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Drawing marked to show revision

FIGURE 9A

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   1 cggcacgagc ggcacgagag aagagactcc aatcgacaag aagctggaaa agaatgatgt
  61 tgtccttaaa caacctacag aatatcatct ataacccggt aatcccgttt gttggcacca
 121 ttcctgatca gctggatcct ggaactttga ttgtgatacg tgggcatgtt cctagtgacg
 181 cagacagatt ccaggtggat ctgcagaatg gcagcagcgt gaaacctcga gccgatgtgg
 241 cctttcattt caatcctcgt ttcaaaaggg ccggctgcat tgtttgcaat actttgataa
 301 atgaaaaatg gggacgggaa gagatcacct atgacacgcc tttcaaaaga gaaaagtctt
 361 ttgagatcgt gattatggtg ctgaaggaca aattccaggt ggctgtaaat ggaaaacata
 421 ctctgctcta tggccacagg atcggcccag agaaaataga cactctgggc atttatggca
 481 aagtgaatat tcactcaatt ggttttagct tcagctcgga cttacaaagt acccaagcat
 541 ctagtctgga actgacagag atagttagag aaaatgttcc aaagtctggc acgccccagc
 601 ttagcctgcc attcgctgca aggttgaaca cccccatggg ccctggacga actgtcgtcg
 661 ttcaaggaga agtgaatgca aatgccaaaa gctttaatgt tgacctacta gcaggaaaat
 721 caaaggatat tgctctacac ttgaacccac gcctgaatat taaagcattt gtaagaaatt
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 841 ctgggatgta ctttgagatg ataatttatt gtgatgttag agaattcaag gttgcagtaa
 901 atggcgtaca cagcctggag tacaaacaca gatttaaaga gctcagcagt attgacacgc
 961 tggaaattaa tggagacatc cacttactgg aagtaaggag ctggtagcct acctacacag
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1141 gggtgttctc agtccttgcc atgacgtatg gtggtgtcta gcactgaatg gggaaactgg
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1621 ttttctttat cgtaataaac atgtggctct attagctgca agctttacca agtaattggc
1681 atgacatctg agcacagaaa ttaagccaaa aaaccaaagc aaaacaaata catggtgctg
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1801 tcagagtcta cacagacgcc tacagaagtt tcaggaagag ccaagatgca ttcaatttgt
1861 aagatattta tggccaacaa agtaaggtca ggattagact tcaggcattc ataaggcagg
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1981 atctgttttg ttcccatgaa atcaccaatc aaggcctccg ttcttctaaa gattagtcca
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2161 gaagttccat gtatatggga tctttacagg tcagatcttg ttacaggaaa tttcaaaggt
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2281 agaactctgc caggatttag gaatattttc agaacagatt ttagatatta tttctatcca
2341 tatattgaaa aggaatacca ttgtcaatct tatttttta aaagtactca gtgtagaaat
2401 cgctagccct taattctttt ccagcttttc atattaatgt atgcagagtc tcaccaagct
2461 caaagacact ggttgggggt ggagggtgcc acagggaaag ctgtagaagg caagaagact
2521 cgagaatccc ccagagttat ctttctccat aaagaccatc agagtgctta actgagctgt
2581 tggagactgt gaggcattta ggaaaaaaat agcccactca catcattcct tgtaagtctt
2641 aagttcattt tcattttacg tggaggaaaa aaatttaaaa agctattagt atttattaat
2701 gaatttttact gagacatttc ttagaaatat gcacttctat actagcaagc tctgtctcta
2761 aaatgcaagt tggccttttg cttgccacat ttctgcatta aacttctata ttagcttcaa
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3001 gttcttagtt aaccaccaat ggaactgggt tcattctgaa tcctggagga gcttcctcgt
3061 gccacccagt gtttctgggc cctctgtgtg agcagccagg tgtgagctgt tttagaagca
3121 gcgtgttgcc ttcatctctc ccgtttccca aaagaacaaa ggataaaggt gacagtcaca
3181 ctcctgggtt aaaaaaagca ttccagaacc acttctcttt atgggcacaa caacaaagaa
3241 gctaagttcg cctacccaaa tgaaagtagg ctttacagtc aagtacttct gttgattgct
3301 aaataacttc attttcttga aatagagcaa ctttgagtga aatctgcaac atggatacca
3361 tgtatgtaag atactgctgt acagaagagt taaggcttac agtgcaaatg aggcgtcagc
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Drawing marked to show revision.

FIGURE 9 ~~(CONT'D.)~~ B

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3541 gctctatagc ataggcagga gaggcttatg tggcagcaca agccaggtgg ggattttgta
3601 aagaagtgat aaaacatttg taagtaatcc aagtaggaga tattaaggca ccaaaagtaa
3661 catggcaccc aacacccaaa aataaaaata tgaaatatga gtgtgaactc tgagtagagt
3721 atgaaacacc acagaaagtc ttagaaatag ctctggagtg gctctcccag gacagtttcc
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3841 aaaaaaaaaa
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